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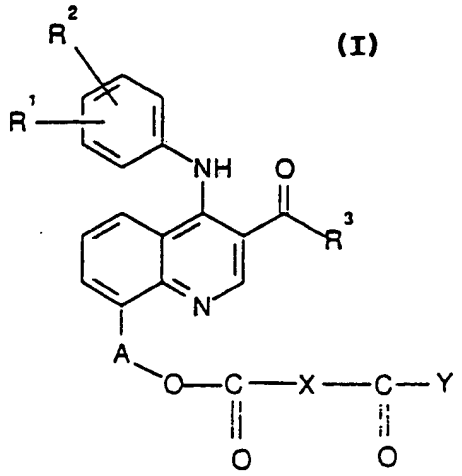

(I)

(57) Abstract

A compound of formula (I), wherein R^1 denotes hydrogen, hydroxyl (OH), halogen or C_{1-4}alkyl, R^2 denotes hydrogen or C_{1-4}alkyl, R^3 denotes C_{1-4}alkyl, A denotes methylene(-CH_2-), ethylene (-CH_2CH_2-), ethylidene [-$CH(CH_3)$-], trimethylene (-$CH_2CH_2CH_2$-), oxyethylene (-O-CH_2CH_2-) or oxytrimethylene (-O-$CH_2CH_2CH_2$-), X denotes C_{1-6}alkylene or C_{2-4}alkenylene and Y denotes hydroxyl (OH) or amino (NH_2), or a salt thereof, processes for their preparation, pharmaceutical compositions containing them and their use in therapy as inhibitors of gastric acid secretion.

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4-Amino-3-acyl quinoline derivatives and their use as inhibitors of gastric acid secretion.

Field of use of the invention

The invention relates to new quinoline derivatives, processes for their preparation, their use and medicaments containing them. The compounds according to the invention are used in the pharmaceutical industry for the preparation of medicaments.

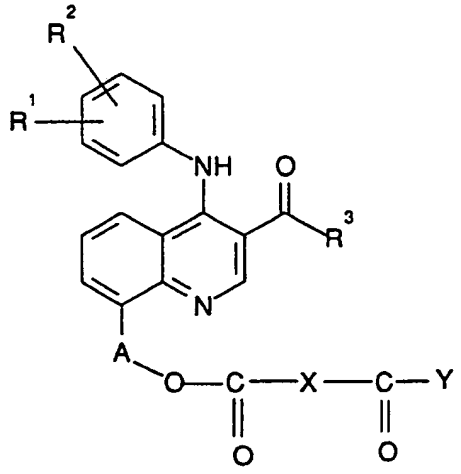
Known technical background

4-Amino-3-acyl-quinoline derivatives and their use as inhibitors of gastric acid secretion are described in European Patent Application EP-A-330 485.

Description of the invention

It has now been found that the compounds which are described below in more detail and which differ from the compounds of the prior art in particular by the substituent in the 8-position of the quinoline ring have surprising and particularly advantageous properties.

The invention thus relates in a first aspect to compounds of the formula I:



(I)

wherein

R^1 denotes hydrogen, hydroxyl (OH), halogen or C_{1-4}alkyl,

R^2 denotes hydrogen or C_{1-4}alkyl,

R^3 denotes C_{1-4}alkyl,

A denotes methylene ($-CH_2-$), ethylene ($-CH_2CH_2-$), ethylidene [$-CH(CH_3)-$], trimethylene ($-CH_2CH_2CH_2-$), oxyethylene ($-O-CH_2CH_2-$) or oxytrimethylene ($-O-CH_2CH_2CH_2-$),

X denotes C_{1-6}alkylene or C_{2-4}alkenylene and

Y denotes hydroxyl (OH) or amino (NH_2),

and their salts.

Halogen in the sense of the present invention is bromine, chlorine and in particular fluorine.

C_{1-4}alkyl represents straight-chain or branched alkyl radicals having 1 to 4 carbon atoms. Examples which may be mentioned are the butyl, iso-butyl, sec-butyl, tert-butyl, propyl, isopropyl, ethyl and the methyl radical. The C_{1-4}alkyl radicals R^1 and/or R^2 are preferably methyl radicals. Preferred C_{1-4}alkyl radicals R^3 are the ethyl, the isopropyl and in particular the propyl radical.

C_{1-6}alkylene represents straight-chain or branched alkylene radicals having 1 to 6 carbon atoms. Examples which may be mentioned are the methylene ($-CH_2-$), ethylene ($-CH_2CH_2-$), ethylidene [$-CH(CH_3)-$], isopropylidene [$-CH(CH_3)_2-$], propylidene [$-CH(C_2H_5)-$], trimethylene ($-CH_2CH_2CH_2-$), propylene [$-CH(CH_3)-CH_2-$], tetramethylene ($-CH_2CH_2CH_2CH_2-$), 1,1-dimethylethylene [$-C(CH_3)_2-CH_2-$], 1,2-dimethylethylene [$-CH(CH_3)-CH(CH_3)-$], 1-methyltrimethylene [$-CH(CH_3)-CH_2CH_2-$], 2-methyltrimethylene [$-CH_2-CH(CH_3)-CH_2-$], pentylidene [$-CH(C_4H_9)-$], pentan-3-ylidene [$-CH(C_2H_5)_2-$], pentamethylene ($-CH_2CH_2CH_2CH_2CH_2-$), and the hexamethylene radical ($-CH_2CH_2CH_2CH_2CH_2CH_2-$), of which the ethylene radical is preferred.

C_{2-4}alkenylene represents straight-chain or branched, mono- or polyunsaturated alkenylene radicals having 1 to 4 carbon atoms. Examples which may be mentioned are the vinylene ($-CH=CH-$), propenylene ($-CH_2-CH=CH-$), isopropenylene [$-CH_2-C(=CH_2)-$], 2-butenylene ($-CH_2-CH=CH-CH_2-$) and the 1,3-butadienylene radical ($-CH=CH-CH=CH-$), of which the vinylene radical is preferred.

Since the compounds of the formula I are ampholytes, possible salts are both acid addition salts and salts with bases. The pharmacologically tolerated salts of the inorganic and organic acids and bases usually used in pharmaceutical formulations may be mentioned in particular. Salts which are not tolerated pharmacologically and which may initially be obtained as process products, for example, when the compounds according to

the invention are prepared on an industrial scale are converted into pharmacologically tolerated salts by processes known to the expert.

Examples of such suitable salts are water-soluble and water-insoluble acid addition salts with acids such as, for example, hydrochloric acid, hydrobromic acid, phosphoric acid, nitric acid, sulphuric acid, acetic acid, citric acid, D-gluconic acid, benzoic acid, 2-(4-hydroxybenzoyl)-benzoic acid, butyric acid, sulphosalicylic acid, maleic acid, lauric acid, malic acid, fumaric acid, succinic acid, oxalic acid, tartaric acid, embonic acid, stearic acid, toluenesulphonic acid, methanesulphonic acid or 3-hydroxy-2-naphthoic acid, the acids being employed in the salt preparation in an equimolar ratio or a ratio which deviates therefrom - depending on whether the acid is mono- or polybasic and depending on what salt is desired. Examples of basic salts which may be mentioned are lithium, sodium, potassium, calcium, aluminium, magnesium, titanium, ammonium or guanidinium salts, it also being possible here for the bases to be employed in the salt preparation in an equimolar ratio or a ratio which deviates therefrom.

Compounds of the formula I which are to be singled out are those in which

R^1 denotes hydrogen, hydroxyl (OH) or fluorine,

R^2 denotes methyl,

R^3 denotes ethyl, propyl or isopropyl,

A denotes methylene ($-CH_2-$), ethylene ($-CH_2CH_2-$), ethylidene [$-CH(CH_3)-$] or oxyethylene ($-O-CH_2CH_2-$),

X denotes methylene ($-CH_2-$), ethylene ($-CH_2CH_2-$) or vinylene (-CH=CH-) and

Y denotes hydroxyl (OH),

and their salts.

Compounds of the formula I which are to be singled out in particular are those in which

R^1 is in the 4-position relative to the -NH- group and denotes hydrogen, hydroxyl (OH) or fluorine,

R^2 is in the 2-position relative to the -NH- group and denotes methyl,

A denotes methylene ($-CH_2-$) or oxyethylene ($-O-CH_2CH_2-$),

X denotes ethylene ($-CH_2CH_2-$) and

Y denotes hydroxyl (OH),

and their salts.

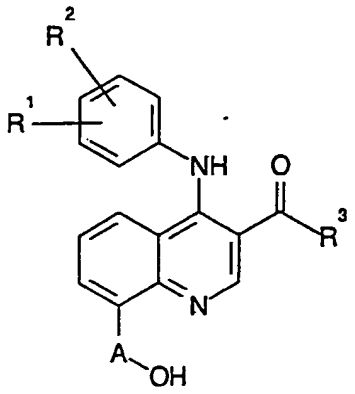
One or more chiral centres may be present in the compounds of the formula I, depending on the nature of the substituents. The invention relates to all the enantiomers and diastereomers as well as mixtures and racemates thereof.

Examples of compounds of the formula I according to the invention are summarised in the following Table 1 with the aid of selected meanings of R^1, R^2, R^3, A, X and Y:

Table 1

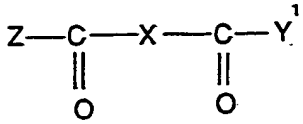
	R^1	R^2	R^3	A	X	Y
	4-H	2-CH_3	-CH_2CHCH	-OCH_2CH_2-	-CH_2-	OH
	4-H	2-CH_3	-CH_2CHCH	-OCH_2CH_2-	-CH_2CH_2-	OH
	4-H	2-CH_3	-CH_2CHCH	-OCH_2CH_2-	-CH_2CH_2-	NH_2
	4-H	2-CH_3	-CH_2CHCH	-OCH_2CH_2-	-CH=CH-	OH
	4-H	2-CH_3	-CH_2CHCH	-OCH_2CH_2-	-$CH(CH_3)$-	OH
	4-H	2-CH_3	-CH_2CHCH	-OCH_2CH_2-	-$C(CH_3)_2$-	OH
	4-H	2-CH_3	-CH_2CHCH	-OCH_2CH_2-	-$CH(CH_2CH_3)$-	OH
	4-H	2-CH_3	-CH_2CHCH	-OCH_2CH_2-	-$CH_2CH_2CH_2$-	OH
	4-H	2-CH_3	-CH_2CHCH	-OCH_2CH_2-	-$CH(CH_3)CH_2$-	OH
	4-OH	2-CH_3	-CH_2CHCH	-OCH_2CH_2-	-CH_2-	OH
	4-OH	2-CH_3	-CH_2CHCH	-OCH_2CH_2-	-CH_2CH_2-	OH
	4-OH	2-CH_3	-CH_2CHCH	-OCH_2CH_2-	-CH=CH-	OH
	4-F	2-CH_3	-CH_2CHCH	-OCH_2CH_2-	-CH_2-	OH
	4-F	2-CH_3	-CH_2CHCH	-OCH_2CH_2-	-CH_2CH_2-	OH
	4-F	2-CH_3	-CH_2CHCH	-OCH_2CH_2-	-CH=CH-	OH
	4-H	2-CH_3	-CH(CHCH	-OCH_2CH_2-	-CH_2-	OH
	4-H	2-CH_3	-CH(CHCH	-OCH_2CH_2-	-CH_2CH_2-	OH
	4-H	2-CH_3	-CH(CHCH	-OCH_2CH_2-	-CH=CH-	OH
	4-H	2-CH_3	-CH_2CH	-OCH_2CH_2-	-CH_2-	OH
	4-H	2-CH_3	-CH_2CH	-OCH_2CH_2-	-CH_2CH_2-	OH
	4-H	2-CH_3	-CH_2CH	-OCH_2CH_2-	-CH=CH-	OH
	4-H	2-CH_3	-CH_2CHCH	-CH_2-	-CH_2-	OH
	4-H	2-CH_3	-CH_2CHCH	-CH_2-	-CH_2CH_2-	OH
	4-H	2-CH_3	-CH_2CHCH	-CH_2-	-CH=CH-	OH
	4-H	2-CH_3	-CH_2CHCH	-CH_2CH_2-	-CH_2-	OH
	4-H	2-CH_3	-CH_2CHCH	-CH_2CH_2-	-CH_2CH_2-	OH
	4-H	2-CH_3	-CH_2CHCH	-CH_2CH_2-	-CH=CH-	OH
	4-H	2-CH_3	-CH_2CHCH	-$CH(CH_3)$-	-CH_2-	OH
	4-H	2-CH_3	-CH_2CHCH	-$CH(CH_3)$-	-CH_2CH_2-	OH
	4-H	2-CH_3	-CH_2CHCH	-$CH(CH_3)$-	-CH=CH-	OH
	4-OH	2-CH_3	-CH_2CHCH	-CH_2-	-CH_2-	OH
	4-OH	2-CH_3	-CH_2CHCH	-CH_2-	-CH_2CH_2-	OH
	4-OH	2-CH_3	-CH_2CHCH	-CH_2-	-CH=CH-	OH
	4-F	2-CH_3	-CH_2CHCH	-CH_2-	-CH_2-	OH
	4-F	2-CH_3	-CH_2CHCH	-CH_2-	-CH_2CH_2-	OH
	4-F	2-CH_3	-CH_2CHCH	-CH_2-	-CH=CH-	OH

The invention furthermore relates to a process for the preparation of the compounds according to the invention and their salts. The process is characterised in that compounds of the formula II



(II)

wherein R^1, R^2, R^3 and A are as described for formula (I), are reacted with dicarboxylic acid derivatives of the formula III



(III)

wherein X is as described for formula (I), Y^1 is a group Y as described for formula (I) or a protected group Y, and Z represents OH (hydroxyl) or a suitable leaving group, or wherein Y and Z together denote an oxygen atom (cyclic anhydride), and in that, if desired, the resulting compounds I are then converted into their salts, or in that, if desired, the compounds I are then liberated from resulting salts of the compounds I.

Suitable protected groups Y include protected hydroxy groups as known to those skilled in the art, in particular benzyloxy groups.

The reaction of the compounds II with the dicarboxylic acid derivatives III is carried out in a manner which is known per se, such as is known to the expert on the basis of his specialised knowledge of esterification reactions. The esterification is carried out in inert solvents, such as, for example, dioxane or tetrahydrofuran, and, depending on the nature of the group Z, either in the presence of a dehydrating agent or an agent which bonds water chemically, such as, for example, dicyclohexylcarbodiimide (if Z = OH), or

in the presence of an auxiliary base (e.g. triethylamine), if Z represents a leaving group, for example a halogen atom (in particular chlorine). The leaving group Z is preferably an alkoxycarbonyloxy radical (mixed anhydride), in particular the isobutoxycarbonyloxy radical, in which case the reaction can be carried out without further addition of a dehydrating agent. Particularly preferred is the reaction of compounds II with (cyclic) dicarboxylic acid anhydrides III (Y and Z together denote an oxygen atom).

The compounds of the formula II are known from EP-A-330 485.

The following examples illustrate the invention in more detail, without limiting it. The invention preferably relates to the new compounds mentioned by name in the examples and the salts of these compounds. M.p. denotes melting point, the abbreviation h is used for hour(s) and the abbreviation min is used for minutes. "Ether" is understood as meaning diethyl ether.

Example 1

Succinic acid mono-{2-[3-butyryl-4-(2-methylphenylamino)-quinolin-8-yl]-oxyethyl} ester

a) 3-Butyryl-4-(2-methylphenylamino)-8-(2-hydroxyethoxy)-quinoline sodium salt

A solution of 1.83 g (5mmol) 3-butyryl-4-(2-methylphenylamino)-8-(2-hydroxyethoxy)-quinoline in anhydrous tetrahydrofuran (50 ml) is added dropwise to a suspension of 300 mg (10 mmol) sodium hydride in anhydrous tetrahydrofuran (10 ml) at room temperature in the course of 30 min, while stirring vigorously. The mixture is subsequently stirred at room temperature for a further 2 h. The solution is then employed directly in step b).

b) Succinic acid mono-{2-[3-butyryl-4-(2-methylphenylamino)-quinolin-8-yl]-oxyethyl ester}

A solution of 0.7 ml (6.3 mmol) N-methylmorpholine in 10 ml tetrahydrofuran is added to a solution of 1.49 g (12.5 mmol) succinic acid in anhydrous tetrahydrofuran (50 ml) and the mixture is stirred at room temperature for 30 min. A solution of 0.82 ml (6.25 mmol) isobutyl chloroformate in 10 ml tetrahydrofuran is then added dropwise in the course of 30 min. The suspension is subsequently stirred at room temperature for a further 90 min. The solution prepared in a) is then added dropwise at room temperature in the course of 30 min. The yellow suspension is stirred at room temperature for a further 3 days. Water (150 ml) is then added and the mixture is extracted with ethyl acetate (4 x 150 ml). The organic extracts are washed with water (200 ml), dried over magnesium sulphate and concentrated. The residue is purified by chromatography on silica gel (mobile phase: methylene chloride/methanol = 9:1). The fractions of mRf = 0.25 are concentrated. After crystallisation from ethyl acetate, 1.21 g (52%) of the title compound are isolated. M.p.: 146-148°C.

Example 2

Succinic acid mono-{2-[3-butyryl-4-(2-methylphenylamino)-quinolin-8-yl]-oxyethyl} ester

A mixture of 1.00 g (2.75 mmol) 3-butyryl-4-(2-methylphenylamino)-8-(2-hydroxyethyl)-quinoline and 3.64 mg (3.57 mmol) 98% succinic anhydride in 12 ml

anhydrous tetrahydrofuran is stirred under reflux for 9 h, whereupon the product begins to crystallise. 20 ml of diisopropyl ether are added dropwise, and the mixture is cooled and stirred for 1.5 h in an ice bath. The yellow precipitate is filtered off and washed with diisopropyl ether. 1.21 g (95.1%) of the title compound of m.p. 163-164°C are obtained.

When the reaction is carried out analogously in the presence of 2.74 mmol potassium tert-butoxide at room temperature, the potassium salt of the title compound is obtained.

Example 3

Glutaric acid mono-{2-[3-butyryl-4-(2-methylphenylamino)-quinolin-8-yloxy]ethyl} ester

1.00 g (2.74 mmol) 3-butyryl-4-(2-methylphenylamino)-8-(2-hydroxyethoxy)-quinoline and 407 mg (3.57 mmol) glutaric anhydride were reacted analogously to Example 2. The solution was concentrated in vacuo, diisopropyl ether added, and 1.22 g (92.8%) of the title compound of m.p. 160-161°C obtained.

Example 4

3-Methylglutaric acid mono-{2-[3-butyryl-4-(2-methylphenylamino)-quinolin-8-yloxy]ethyl} ester

2.00 g (5.49 mmol) 3-butyryl-4-(2-methylphenylamino)-8-(2-hydroxyethoxy)-quinoline, 0.91 g (6.3 mmol) 99% 3-methylglutaric anhydride and 60 ml dry tetrahydrofuran were heated under reflux for 24 h. The mixture was stirred at room temperature for 12 h, cooled in ice, filtered and dried in vacuo at 100°C. 2.40 g (88.7%) of the title compound of m.p. 160-162°C were obtained.

Example 5

3,3-Dimethylglutaric acid mono-{2-[3-butyryl-4-(2-methylphenylamino)-quinolin-8-yloxy]ethyl} ester

Using 3,3-dimethylglutaric anhydride analogously to Example 4, 27% of the title compound of m.p. 151-156°C was obtained after heating under reflux for 48 h, concentration in vacuo and chromatography on silica gel using ethyl acetate.

Example 6

2,2-Dimethylglutaric acid 5-mono-{2-[3-butyryl-4-(2-methylphenylamino)-quinolin-8-yloxy]ethyl} ester

From 1.82 g (5.0 mmol) 3-butyryl-4-(2-metylphenylamino)-8-(2-hydroxyethoxy)-quinoline and 930 mg 2,2-dimethylglutaric anhydride in 60 ml dry tetrahydrofuran, 2.14 g (84.6%) of the title compound of m.p. 179-180°C were obtained analogously to Example 4 and after recrystallisation from ethyl acetate (260 ml).

Example 7

Malonic acid mono-{2-[3-butyryl-4-(2-methylphenylamino)-quinolin-8-yloxy]ethyl} ester

A solution of 0.53 ml (5.5 mmol) malonic acid dichloride in 10 ml tetrahydrofuran was added dropwise to a solution of 2.00 g (5.49 mmol) 3-butyryl-4-(2-methylphenylamino)-8-(2-hydroxyethoxy)-quinoline in 40 ml dry tetrahydrofuran at 0°C in the course of 30 min, and the mixture stirred at room temperature for 4 h, and then poured onto ice/water, buffered to pH 5.7 with sodium bicarbonate and extracted with isopropyl acetate. The organic solution was dried with magnesium sulphate and concentrated in vacuo. Column chromatography with ethyl acetate/isopropanol 2:1 over 1,600 g silica gel followed by concentration and precipitation with diisopropyl ether gave 1.7 g (68.8%) of the title compound of m.p. 186-187°C (decomposition).

Example 8

Succinic acid mono-{2-(3-butyryl-4-(4-fluoro-2-methylphenylamino)-quinolin-8-yl)oxyethyl} ester

a) Benzyl succinic acid mono-{2-(3-butyryl-4-(4-fluoro-2-methylphenylamino)-quinolin-8-yl)oxyethyl} ester

Isobutyl chloroformate (1.43 ml, 11 mmol) was added to a mixture of benzyl hydrogen succinate (2.29 g, 11 mmol), triethylamine (1.53 ml, 11 mmol), dioxan (100 ml) and chloroform (50 ml). The resulting suspension was stirred for 30 min at room temperature, then 3-butyryl-4-(4-fluoro-2-methylphenylamino)-8-(2-hydroxyethoxy)-

quinoline (3.5 g, 9.2 mmol) and triethylamine (1.53 ml, 11 mmol) were added, and the mixture was heated at reflux for 16 hours. The solvent was evaporated, and the residue was taken up in dichloromethane, washed with aqueous sodium bicarbonate then with water, dried, and the solvent evaporated. Chromatography (silica, dichloromethane/methanol) and trituration with ether gave the product (1.77 g, 34%); m.p. 107-111°C.

b) Succinic acid mono-{2-(3-butyryl-4-(4-fluoro-2-methylphenylamino)-quinolin-8-yl)oxyethyl} ester

A solution of benzyl succinic acid mono-{2-(3-butyryl-4-(4-fluoro-2-methylphenylamino)-quinolin-8-yl)-oxyethyl} ester (1.7 g, 3.0 mmol) in glacial acetic acid (100 ml) was hydrogenated at 50 psi over 10% palladium on charcoal (0.1 g) for 5 hours, then filtered and the solvent removed *in vacuo*. Recrystallisation from ethyl acetate gave the product (1.1 g, 77%); m.p. 172-174°C.

Example 9

Succinic acid mono-{2-(3-butyryl-4-(4-fluoro-2-methylphenylamino)-quinolin-8-yl)oxyethyl} ester

a) Benzyl succinic acid mono-{2-(3-propanoyl-4-(2-methylphenylamino)-quinolin-8-yl)oxyethyl} ester

Isobutyl chloroformate (1.95 ml, 15 mmol) was added to a mixture of benzyl hydrogen succinate (3.12 g, 15 mmol), triethylamine (1.95 ml, 15 mmol), dioxan (150 ml) and chloroform (100 ml). The resulting suspension was stirred for 30 min at room temperature, then 3-propanoyl-4-(2-methylphenylamino)-8-(2-hydroxyethoxy)quinoline (3.5 g, 10 mmol) and triethylamine (1.95 ml, 15 mmol) were added, and the mixture was heated at reflux for 16 hours. The solvent was evaporated, and the residue was taken up in dichloromethane, washed with aqueous sodium bicarbonate then with water, dried, and the solvent evaporated. Trituration with ether gave the product (1.55 g, 29%); m.p. 108-110°C.

b) Succinic acid mono-{2-(3-propanoyl-4-(2-methylphenylamino)-quinolin-8-yl)oxyethyl} ester

A solution of benzyl succinic acid mono-{2-(3-propanoyl-4-(2-methylphenylamino)-quinolin-8-yl)oxyethyl} ester (1.55 g, 2.87 mmol) in glacial acetic acid (100 ml) was hydrogenated at 50 psi over 10% palladium on charcoal (0.1 g) for 5 hours, then filtered and the solvent removed *in vacuo*. Recrystallisation from ethyl acetate gave the product (1.05 g, 81%); m.p. 189-193°C (dec).

Example 10

Succinic acid mono-{2-(3-propanoyl-4-(4-fluoro-2-methylphenylamino)-quinolin-8-yl)oxyethyl} ester

a) Benzyl succinic acid mono-{2-(3-propanoyl-4-(4-fluoro-2-methylphenylamino)-quinolin-8-yl)oxyethyl} ester

Isobutyl chloroformate (1.43 ml, 11 mmol) was added to a mixture of benzyl hydrogen succinate (2.29 g, 11 mmol), triethylamine (1.53 ml, 11 mmol), tetrahydrofuran (50 ml) and chloroform (10 ml). The resulting suspension was stirred for 20 min at room temperature, then 3-propanoyl-4-(4-fluoro-2-methylphenylamino)-8-(2-hydroxyethoxy)-quinoline (3.68 g, 10 mmol) was added, and the mixture was heated at reflux for 16 hours. The solvent was evaporated, and the residue was taken up in dichloromethane, washed with aqueous sodium bicarbonate then with water, dried, and the solvent evaporated. Chromatography (silica, dichloromethane/methanol) and recrystallisation from methanol gave the product (2.9 g, 47%); m.p. 110-113 C.

b) Succinic acid mono-{2-(3-propanoyl-4-(4-fluoro-2-methylphenylamino)-quinolin-8-yl)oxyethyl} ester

A solution of benzyl succinic acid mono-{2-(3-propanoyl-4-(4-fluoro-2-methylphenylamino)-quinolin-8-yl)oxyethyl} ester (2.7 g, 4.8 mmol) in glacial acetic acid (100 ml) was hydrogenated at 50 psi over 10% palladium on charcoal (0.2 g) for 3 hours, then filtered and the solvent removed *in vacuo*. Recrystallisation from ethyl acetate gave the product (1.4 g, 62%); m.p. 195-197 C.

Commercial usefulness

The compounds of the formula I and their salts have valuable pharmacological properties which render them commercially usable. They display a pronounced inhibition of gastric acid secretion and an excellent protective action on the stomach and intestine in warm-blooded animals. The comparatively good solubility of the compounds according to the invention is of particular importance. On the basis of this good solubility, an even and uniform availability which is essentially independent of the particular secretion status is achieved - a wide range of scatter being avoided.

"Protection of the stomach and intestine" in this connection is understood as meaning the prevention and treatment of gastrointestinal diseases, in particular gastrointestinal inflammatory diseases and lesions (such as e.g. ulcus ventriculi, ulcus duodeni, gastritis, hyperacid irritated stomach or irritated stomach of medicamentous origin) which can be caused, for example, by microorganisms (e.g. Helicobacter pylori), bacterial toxins, medicaments (e.g. certain antiinflammatories and antirheumatics), chemicals (e.g. ethanol), gastric acid or stress situations.

The compounds according to the invention and their salts have proved to have an excellent action on various models in which the antiulcerogenic and the antisecretory properties are determined, and therefore to be outstandingly suitable for use in human and veterinary medicine, in which they are used in particular for the treatment and/or prophylaxis of diseases of the stomach and/or intestine.

The invention thus furthermore relates to the compounds according to the invention and their pharmacologically tolerated salts for use in the treatment and/or prophylaxis of the above-mentioned diseases.

The invention also relates to the use of the compounds according to the invention and their pharmacologically tolerated salts for the preparation of medicaments which are employed for the treatment and/or prophylaxis of the above-mentioned diseases.

The invention furthermore relates to the use of the compounds according to the invention and their salts for the treatment and/or prophylaxis of the above-mentioned diseases.

The invention furthermore relates to medicaments which contain one or more compounds of the formula I and/or their pharmacologically tolerated salts.

The medicaments are prepared by processes which are known per se and with which the expert is familiar. The pharmacologically active compounds (= active compounds) according to the invention are employed as medicaments either as such or, preferably, in combination with suitable pharmaceutical auxiliaries or excipients, in the form of tablets, coated tablets, capsules, suppositories, plasters (e.g. as TTS), emulsions, suspensions or solutions, the active compound content advantageously being between 0.1 and 95%.

The expert is familiar, on the basis of his specialised knowledge, with the auxiliaries and excipients which are suitable for the medicament formulations desired. In addition to solvents, gel-forming agents, suppository bases, tablet auxiliaries and other active compound excipients, it is possible to use, for example, antioxidants, dispersing agents, emulsifiers, foam suppressants, flavour correctants, preservatives, solubilizing agents, dyestuffs or, in particular, permeation promoters and complexing agents (e.g. cyclodextrins).

The active compounds can be administered orally, parenterally or percutaneously.

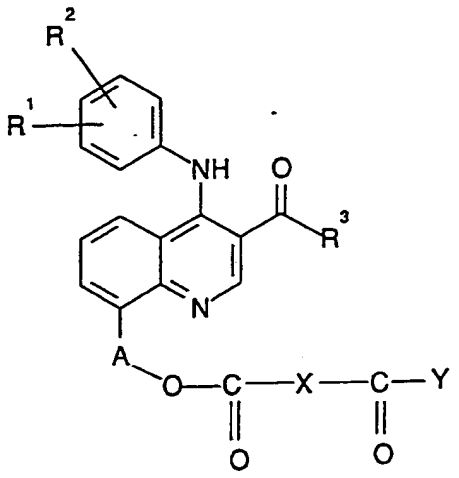
In general, in the case of oral administration, for the active compound or compounds to be administered in a daily dose of about 0.01 to about 20, preferably 0.05 to 5, in particular 0.1 to 1.5 mg/kg body weight, if appropriate in the form of several, preferably 1 to 4, individual doses, in order to achieve the desired results. For parenteral treatment, similar or (especially in the case of intravenous administration of the active compounds) as a rule lower dosages can be used. The particular optimum dosage and mode of administration required for the active compounds can easily be determined by any expert on the basis of his specialised knowledge.

If the compounds and/or salts according to the invention are to be employed for the treatment of the above-mentioned diseases, the pharmaceutical formulations can also contain one or more pharmacologically active constituents from other groups of medicaments, such as antacids, for example aluminium hydroxide or magnesium aluminate; tranquillisers, such as benzodiazepines, for example diazepam; spasmolytics, such as e.g. bietamiverine or camylofin, or anticholinergics, such as e.g. oxyphencyclimine or phencarbamide; local anaesthetics, such as e.g. tetracaine or procaine; and, if appropriate, also enzymes, vitamins or amino acids.

There should be singled out in this connection in particular combination of the compounds according to the invention with drugs which inhibit acid secretion, such as for example, H_2-blockers (e.g. cimetidine or ranitidine) or furthermore with so-called peripheral anticholinergics (e.g. pirenzepine or telenzepine) as well as with gastrin antagonists, with the aim of intensifying the main action in the additive or superadditive sense and/or of eliminating or reducing the side effects, or furthermore combination with antibacterial substances (such as e.g. cephalosporins, tetracyclines, nalidixic acid, penicillins or also bismuth salts) for combating Helicobacter pylori.

Claims

1. A compound of formula I,



(I)

wherein

R^1 denotes hydrogen, hydroxyl (OH), halogen or C_{1-4}alkyl,

R^2 denotes hydrogen or C_{1-4}alkyl,

R^3 denotes C_{1-4}alkyl,

A denotes methylene ($-CH_2-$), ethylene ($-CH_2CH_2-$), ethylidene [$-CH(CH_3)-$], trimethylene ($-CH_2CH_2CH_2-$), oxyethylene ($-O-CH_2CH_2-$) or oxytrimethylene ($-O-CH_2CH_2CH_2-$),

X denotes C_{1-6}alkylene or C_{2-4}alkenylene and

Y denotes hydroxyl (OH) or amino (NH_2),

or a salt thereof.

2. A compound of formula I according to claim 1, wherein

R^1 denotes hydrogen, hydroxyl (OH) or fluorine,

R^2 denotes methyl,

R^3 denotes ethyl, propyl or isopropyl,

A denotes methylene ($-CH_2-$), ethylene ($-CH_2CH_2-$), ethylidene [$-CH(CH_3)-$] or oxyethylene ($-O-CH_2CH_2-$),

X denotes methylene ($-CH_2-$), ethylene ($-CH_2CH_2-$) or vinylene (-CH=CH-) and

Y denotes hydroxyl (OH),

or a salt thereof.

3. A compound of formula I according to claim 1, wherein

R^1 is in the 4-position relative to the -NH- group and denotes hydrogen, hydroxyl (OH) or fluorine,

R^2 is in the 2-position relative to the -NH- group and denotes methyl,

A denotes methylene ($-CH_2-$) or oxyethylene ($-O-CH_2CH_2-$),

X denotes ethylene ($-CH_2CH_2-$) and

Y denotes hydroxyl (OH),

or a salt thereof.

4. A compound according to claim 1 which is

succinic acid mono-{2-[3-butyryl-4-(2-methylphenylamino)-quinolin-8-yl]-oxyethyl} ester,

succinic acid mono-{2-[3-butyryl-4-(2-methylphenylamino)-quinolin-8-yl]-oxyethyl} ester,

glutaric acid mono-{2-[3-butyryl-4-(2-methylphenylamino)-quinolin-8-yloxy]ethyl} ester,

3-methylglutaric acid mono-{2-[3-butyryl-4-(2-methylphenylamino)-quinolin-8-yloxy]ethyl} ester,

3,3-dimethylglutaric acid mono-{2-[3-butyryl-4-(2-methylphenylamino)-quinolin-8-yloxy]ethyl} ester,

2,2-dimethylglutaric acid 5-mono-{2-[3-butyryl-4-(2-methylphenylamino)-quinolin-8-yloxy]ethyl} ester,

malonic acid mono-{2-[3-butyryl-4-(2-methylphenylamino)-quinolin-8-yloxy]ethyl} ester,

succinic acid mono-{2-(3-butyryl-4-(4-fluoro-2-methylphenylamino)-quinolin-8-yl)oxyethyl} ester,

succinic acid mono-{2-(3-butyryl-4-(4-fluoro-2-methylphenylamino)-quinolin-8-yl)oxyethyl} ester, or

succinic acid mono-{2-(3-propanoyl-4-(4-fluoro-2-methylphenylamino)-quinolin-8-yl)oxyethyl} ester

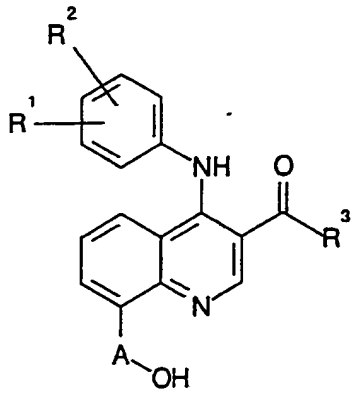
or a salt thereof.

5. A pharmaceutical composition comprising a compound according to any one of claims 1 to 4 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

6. A compound according to any one of claims 1 to 4 for use in therapy.

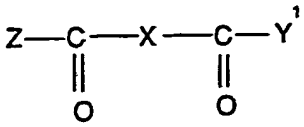
7. A compound according to any one of claims 1 to 4 for use in the inhibition of gastric secretion.

8. A process for the preparation of a compound according to claim 1 which comprises reacting a compound of formula II,



(II)

wherein R^1, R^2, R^3 and A have the meanings given in claim 1, with a dicarboxylic acid derivative of formula III



(III)

wherein X is as described for formula (I), Y^1 is a group Y as described for formula (I) or a protected group Y, and Z represents OH (hydroxyl) or a suitable leaving group, or wherein Y and Z together denote an oxygen atom (cyclic anhydride), and in that, if desired, the resulting compounds I are then converted into their salts, or in that, if desired, the compounds I are then liberated from resulting salts of the compounds I.

INTERNATIONAL SEARCH REPORT

International Application No PCT/EP 92/02898

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 C07D215/44; A61K31/47

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	C07D ; A61K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
Y	EP,A,0 330 485 (SMITHKLINE BECKMAN INTERCREDIT B.V.) 30 August 1989 cited in the application see claims 1-9	1-7
Y	C. HANSCH "COMPREHENSIVE MEDICINAL CHEMISTRY ", FIRST EDITION, VOLUME 5, CHAPTER 23.4 1990, PERGAMON PRESS, LONDON pages 111 - 142; C. M. MACDONALD & R.G. TURCAN: 'Sites of drug metabolism, prodrugs and bioactivation.' see especially chapter 23.4.3.5.4, page 128	1-7

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° Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
12 FEBRUARY 1993	- 4. 03. 93
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	HARTRAMPF G.W.

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category°	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
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A	EP,A,0 416 749 (SMITHKLINE BECKMAN INTERCREDIT B.V.) 13 March 1991 see the whole document	1-8
A	EP,A,0 259 174 (SMITH KLINE & FRENCH LABORATORIES LIMITED) 9 March 1988 see the whole document	1-8
P,Y	WO,A,9 212 969 (SMITHKLINE BEECHAM INTERCREDIT B.V.) 6 August 1992 see the whole document	1-7

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

EP 9202898
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The members are as contained in the European Patent Office EDP file on
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